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Patentanmeldung Nr. | Patent application No. | Demande de brevet n°

98308403.9

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PUFA SUPPLEMENTS

This invention relates to the provision of polyunsaturated fatty acids (PUFAs) in the diet of humans and animals. More specifically it relates to the provision of polyunsaturated fatty acids of the n-6 and the n-3 families, and in particular the n-6 fatty acid arachidonic acid (ARA) and the n-3 fatty acid docosahexaenoic acid (DHA), and ratios thereof in balanced amounts.

The invention is in part based on the finding that an optimal balance of the n-6 and n-3 families can play a significant role in health and the prevention of chronic diseases. The main reason for this is that the two families compete for the same enzyme activities for the formation of the long-chain members from their C18 precursors. As a consequence, and this occurs in prior art compositions, a surplus of member(s) of one family tends to depress the amount of the other family. Moreover, the members of the two families can have opposing effects on essential functions in the body, such as blood clotting and the immune response.

Introduction

It is technologically relatively easy to provide the C18 n-6 fatty acid linoleic acid to the diet, since this fatty acid is abundantly present in common oils of vegetable origin, such as corn oil and soy oil. There are also plant oils available that contain the C18 n-3 fatty acid alpha-linolenic acid, for instance rape seed oil, but these are much less readily used due to their lower stability. This usually leads to a surplus of the n-6 family over the n-3 family in the modern diet.

It has therefore been argued that n-3 fatty acids should be supplemented in many cases where a relative depletion is suspected. Generally this cannot be achieved by providing the C-18 precursor, since the efficiency of conversion to C20 and C22 derivatives is low. Therefore, the consensus is that the C20 and C22 n-3 fatty acids (EPA and DHA) should be provided themselves.

In many cases the rationale behind this supplementation is to attenuate the action of the long-chain n-6 fatty acid ARA. It has been shown that the addition of the n-3 PUFAs, either derived from fish oil or from microbial (algae) oils indeed leads to lower ARA levels. In the case of fish oil this occurs in spite of the fact that fish oil contains low amounts of ARA.

This depression of the ARA content is not always desirable. The invention seeks to provide preparations that may enhance the DHA and/or EPA status of animal systems, without adversely affecting ARA levels, or, conversely, enhance ARA without affecting the DHA and/or EPA status.

The use of preparations containing both ARA and n-3 PUFAs has been described before in the provision of PUFAs to infant formula. The rationale behind this is that human breast milk contains appreciable amounts of ARA and DHA which are considered useful to the developing infant.

In contrast, for adult nutrition there is no such natural source, although both ARA and DHA can be found as components of the human diet. However, for a number of ~~reasons these PUFA levels appear to be sub-optimal. Furthermore different populations~~ have different levels of these PUFAs and this can affect the suitable dosage. As there is no model from nature, the relative amounts of PUFAs to be used needs to be determined and the present invention seeks to address this problem and provide various formulations

and proportions of the PUFAs for certain applications.

Prior Art

WO-A-96/37200 (Scotia Holdings) refers to the use of DHA as a pharmaceutical composition, and in particularly either DHA or the precursor thereof for combatting dyslexia or night vision. It refers to granules or powders having 50mg DHA and 50mg ARA, or oils that contain 5% DHA, 5% EPA and 5% ARA for use as salad oils.

WO-A-96/38051 (Suntory) refers to fowl eggs with high ARA and optionally high DHA content resulting from feeding the poultry with n-6 and n-3 fatty acids.

WO-A-92/13086 (Martek Corporation) refers to processes for the production of an ARA-containing oil (ARASCO) and suggests that this oil can be supplied to newborn infants by supplementing infant formula with the oil in an amount similar to that in human breast milk (about 0.59%), and for treating deficiencies in pregnant or nursing women.

M. Makrides *et al*, European Journal of Chemical Nutrition 50:352-357 (1996) refers to a study to assess the effect of varying the internal intake of DHA (from 0 to 1.3g DHA/day) on breast milk fatty acids. It was found that DHA in the diet fed to lactating mothers had a strong specific and dose-dependent effect on breast milk DHA. However, this was found not to affect ARA levels. This study is based on the oils obtained from algae that are available from Martek Corporation, USA, sold under the brand name NEUROMINS™.

WO-A-92/12711 (Martek) refers to oil blends containing ARA and DHA, for example an ARA:DHA ratio of 3:1 to 2:1, in particular to provide levels of these PUFAs in infant formula in amounts comparable to human breast milk having an ARA level of

0.5 to 0.6%).

A number of PUFA-containing compositions are currently marketed. EFANATAL™ are capsule compositions, where it is intended to take two capsules per day to give a daily intake of DHA (125mg), ARA (8.6mg) and GLA (40mg). The capsules contain an oil that is primarily based on fish oil. The Applicant has found that this decreases the *in vivo* ARA content, because the DHA content relative to the ARA content in the product is too high. Thus this product is in fact an ARA lowering, rather than ARA increasing, composition despite the fact that it contains ARA. A comparison between this product and those of the invention are provided later.

EFAMARINE™ is also capsules of primarily fish and evening primrose oils, for which two are to be taken per day to give a daily intake of EPA (34mg), DHA (22mg) and GLA (68mg).

EFALEX™ is an oil blend, where a teaspoon (5ml) is intended to be taken twice a day, each teaspoon giving DHA (100mg), GLA (21mg), ARA (8mg) and thyme oil (6mg).

Summary of the Invention

A first aspect of the present invention relates to an edible formulation comprising ARA at an amount adapted to deliver a dosage (of ARA) of from 150mg to 1g per day.

Preferably the formulation is adapted to deliver from 200 to 900mg per day ARA, such as from 200 to 700mg per day, optimally from 250 to 500mg per day.

~~The edible formulation includes dietary supplements and pharmaceutical~~ formulations and preparations, such as tablets, pills and capsules.

Edible formulations additionally include (solid or liquid) foodstuffs, for example dairy products (margarine, butter, milk, yoghurt), bread, cakes; drinks such as beverages

(tea, coffee, cocoa, chocolate drinks), fruit juices, soft (e.g. fizzy) drinks; confectionery; oily foods (snacks, salad dressing, mayonnaise), soups, sauces, carbohydrate-rich foods (rice, noodles, pasta) fish-containing foods, baby foods (such as infant formula, either as a liquid or powder), pet food, and ready prepared or microwaveable foods.

The ARA can be from any suitable source. It may be from a natural (e.g. vegetable or marine) source, or it may be from a microbial source or from a microorganism, such as fungus, bacterium or a yeast.

Suitable fungi are of the order *Mucorales*, for example *Mortierella*, *Pythium* or *Entomophthora*. The preferred source of ARA is from *Mortierella alpina or Pythium insidiosum*. Suitable commercially available ARA oils include those from Gist-brocades, Wateringseweg, P.O. Box 1, 2600 MA, Delft, The Netherlands under the trade name OPTIMAR™ and ARASCO™ from Martek Corporation, 6480 Dobbin Road, Columbia, MD 21045, United States of America.

In addition to the ARA, one or more additional PUFAs may be provided. This may be another n-6 PUFA in addition to ARA (such as a C18, C20 or C22 fatty acid) or it may be a n-3 fatty acid (for example, a C18, C20 or C22 fatty acid) and in particular EPA and/or DHA. Each PUFA that may be used in the invention may be in the form of a free fatty acid, fatty acid ester (e.g. methyl or ethyl ester) as a phospholipid or as a triglyceride.

If the formulation comprises an n-3 fatty acid, it is preferred that this is EPA or DHA. If it is DHA, then the formulation is preferably adapted to deliver a dosage of from 400 to 600mg per day DHA. Alternatively, or in addition to, if the formulation comprises EPA, then it is preferably adapted to deliver a dosage of from 150mg to 1g per day EPA, such as from 250 to 500mg of EPA per day.

If the formulation comprises more than one PUFA then the amount of each PUFA can be expressed relatively, as a ratio. For example, if an n-3 PUFA is additionally provided, then the ratio of ARA:n-3 PUFA (such as DHA or EPA) is preferably from 1:5 to 5:1, optimally from 1:1 to 1:2.

Preferably the PUFA is present in an oil. This may be a pure oil or a processed (e.g. chemically and/or enzymatically) or concentrated oil. This oil may comprise from 10 to 100%, especially if the oil is almost pure PUFA, but for a microbial oil the content may be from 20 to 45%, optimally from 30 to 45% of the desired PUFA, for example ARA. Of course, this oil may contain one or more PUFAs at these percentage concentrations. The oil may be a single oil derived from a single cell or a microbial source, or it may be a blend or mixture of two or more oils from these or other (e.g. vegetable or marine) sources. The oil may contain one or more antioxidants (e.g. tocopherol, vitamin E, palmitate) for example at a concentration of from 50 to 800ppm, such as 100 to 700ppm. Suitable processes for preparing PUFAs are described in International patent application numbers PCT/EP97/01446 (WO-A-97/36996) and PCT/EP97/01448 (WO-A-97/37032), and PCT/US92/00517 (WO-A-92/13086).

A second aspect of the invention relates to a pharmaceutical composition comprising ARA and DHA at a ratio of ARA:DHA of from 1:1 to 1:2. This ratio of PUFAs has been found to provide a good balance, and increases *in vivo* DHA levels without ARA levels being suppressed due to a too high DHA content. The DHA can be ~~from a natural (e.g. marine) source or from a microbial source (e.g. from an algae).~~

A third aspect relates to a foodstuff comprises from 0.1 to 5% ARA. Preferably, the amount is from 0.2 to 2%, optimally from 0.3 to 0.8%. Suitable foodstuffs have already been discussed in relation to the first aspect. However, particularly preferred foodstuffs

include infant and/or baby foods for example infant formula. Preferred methods of preparing infant formula are disclosed in International application numbers PCT/EP97/01447 (WO-A-97/35487) and PCT/EP97/01449 (WO-A-97/35488).

Suitable formulations can include oils, for example to be taken orally. The oil may be taken as such, or it may be encapsulated, for example in a shell, and may thus be in the form of capsules. The shell or capsules may comprise gelatin and/or glycerol. The formulation may contain other ingredients, for example flavourings (lemon or lime flavours, for example).

A fourth aspect of the present invention relates to the use of ARA as a dietary or nutritional supplement for a woman who is:

a. pregnant and at an age of from 15 to 20;

b. pregnant and at an age of from 40 to 60, such as from 50 to 55;

c. pregnant with her fourth, fifth or subsequent child;

d. pregnant with twins, triplets or quadruplets;

e. pregnant and is from 1 to 3 months into her pregnancy;

f. pregnant as a result of in vitro fertilisation (IVF) or who is undergoing IVF treatment but not yet pregnant;

g. pregnant at from 20 or more weeks of gestation;

h. pregnant and is malnourished, poorly or marginally nourished, suffering from malnutrition or malabsorption;

i. trying to become pregnant;

j. pregnant, for promoting intra-uterine growth of a foetus; or

k. lactating, for increasing the level of ARA or EPA in the women's breast milk.

A fifth aspect relates to the use of ARA as a dietary or nutritional supplement for a human (male or female) over 50 years old, preferably over 65 years old.

A sixth aspect relates to the use of ARA as a dietary or nutritional supplement for a non-human mammal which is pregnant or lactating.

The ARA is preferably ingested at from 150 to 700mg per day, optimally from 250 to 500mg per day.

A seventh aspect of the present invention relates to the use of ARA for the manufacture of a medicament for assisting in preventing, ameliorating or treating a disease or condition associated with an abnormal or low level of an n-3 or n-PUFA, for example in the blood. The invention therefore finds use with people that have low levels of ARA, for example for those that cannot or cannot effectively convert linoleic acid (LA) to ARA. Therefore, suitable patients may have a malfunctioning, inefficient or deficiency in Δ6-desaturase.

The Applicant has found that certain diseases or conditions, in particular neuronal diseases, are associated with low levels of *in vivo* PUFAs, in particular low levels of ARA in the blood. It is therefore thought that the administration of ARA, or a balance of the PUFAs, will be able to assist in the prevention, amelioration or treatment of these diseases or conditions. The diseases in question include: neuronal disease, such as schizophrenia, cystic fibrosis, idiopathic immunoglobulin A nephropathy, multiple sclerosis, retinitis pigmentosis, Usher's syndrome, celiac disease, macular degeneration, ~~Parkinsons' disease, osteoporosis, Alzheimer's disease or phenylketonuria.~~

An eighth aspect relates to the use of ARA, optionally with DHA, for promoting lactation and/or reproductive efficiency, success or fertility in a human or non-human female mammal.

A ninth aspect of the present invention relates to the use of ARA and DHA in a medical formulation at an ARA:DHA ratio that increases the ARA level in blood. Preferably the ratio of ARA:DHA is from 1:5 to 5:1, such as from 1:1 to 1:2.

The invention is particularly application to those people that have low ARA levels, for example diabetics, alcoholics, drug abusers, smokers or people who have an abnormal or low immune level or are immunocompromised.

Preferred features and characteristics of one aspect of the invention are equally applicable to another aspect *mutatis mutandis.*

The following Examples are provided to merely illustrate the invention, and are not to be construed to be limiting.

EXAMPLES

Examples 1 to 3: Preparation of a composition containing balanced proportions of PUFAs.

This example describes the blending of n-6 and n-3 oils so that they can be included in a single capsule.

The composition was prepared by combining one n-6 PUFA-rich oil with three different n-3 PUFA-rich oils. The n-6 PUFA-rich oil was derived from the fermentation of the filamentous fungus *Mortierella alpina*, and contained approximately 40% ARA as the major fatty acid. For the n-3 PUFA-rich oil the three different sources were: a high-EPA (above 45%) low-DHA (about 10%) fish oil (from Pronova, Norway under the trade name EPAX™ , product no. EPAx4510TG), a high-DHA (above 50%) low-EPA (about 20%) fish oil (also from Pronova under the same brand name, product no. EPAx2050TG), and an oil derived from fermentation of the unicellular alga *Crypthecodinium cohnii* which contains 40% DHA as major fatty acid but is virtually devoid of EPA (from Martek Corporation, Columbia, United States of America under the trade name DHASCO™).

The oils were mixed in appropriate quantities to give the desired amounts and proportions of n-3 and n-6 PUFAs. Here the ARA:DHA ratio for the three blends (Examples 1 to 3) was 1:1. During this procedure, the oxidation-sensitive oils were protected from environmental oxygen by a blanket of oxygen-free nitrogen gas. Subsequently, the oils were used to prepare soft-gel gelatin capsules, where each capsule had 400mg ARA and 400mg DHA.

Example 4: Provision of balanced PUFAs to pregnant women during the early or latter stages of pregnancy.

This Example concerns the trial of pregnant women that are supplemented with ARA and DHA either between weeks 6 and 15 or between weeks 20 and 25 during pregnancy until delivery (birth). The ARA source was a triglyceride oil containing 38% ARA available from Gist-brocades, Delft, The Netherlands, under the trade name OPTIMAR™. This is an oil produced by the fungus *Mortierella alpina*. For DHA either a DHA-rich fish oil of food grade or an algae-derived oil obtained from Martek Corporation under the trade mark DHASCOT™ was employed.

Maternal supplementation of ARA and DHA during pregnancy was therefore studied to see if the fatty acid status of the mother measured at birth and subsequently during lactation compared with the controlled group that received no supplementation. The measurements included maternal erythrocyte ARA and DHA values, ARA and DHA content of the umbilical arteries and venous vessel wall, ARA and DHA content of breast milk.

The study was a case controlled study involving 10 pregnant women. One experimental group (of five women) received one or more gelatin capsule (each of 250mg ARA) oil per day (containing 38% ARA) and one capsule (each of 500mg DHA) oil per day (containing 25% DHA). The control group received the same amount of placebo gelatin capsules to overcome differences in daily calorie intake. The vitamin E intake of the experimental and controlled groups was equal, and the capsules were taken during breakfast.

Blood samples were taken at the beginning of the trial and at the end of gestation. Red blood cell fatty acids were measured (as phospholipids) using capillary gas

chromatography with flame ionisation.

It was found that the supplemented women had significantly higher levels of both DHA and ARA in the red blood cells during pregnancy and at the time of birth. Remarkably, these higher levels persisted during the lactation period, being apparent both in the red blood cells of the mothers and their breast milk. The ARA level in breast milk was found to have risen to from 0.8 to 1.0% ARA. In addition the ARA levels in the blood of the newly born children was found to be higher than the control group. This finding is of major significance for mothers and their children under marginal nutritional conditions.

Example 5: Provision of balanced PUFAs to elderly people.

The Applicant perceives a need to enhance the n-3 PUFA status of the population, not in the least in the elderly population, where diseases such as Parkinson's disease and Alzheimer's disease have been found to be associated with a low PUFA status. This is thought to be partly due to inefficient or deficient Δ6-desaturase enzyme. However care is needed, especially in older people, since a decrease in ARA levels could exert a negative effect on the immune system.

A formulation was prepared according to Example 1, containing n-3 and n-6 PUFAs in a ratio of DHA:ARA of 2:1. The capsules were given to a group of healthy, elderly men and women (at least 65 years of age), at a dosage of 1 g n-3 PUFAs per day.

After one month the PUFA status of the red blood cells of the subjects was assessed. It was found that in all cases the levels of DHA had increased, whereas the levels of ARA had remained constant, or showed a slight increase in some cases. Thus it was possible to enhance the n-3 PUFA status of patients, without compromising the ARA status, by the

use of a balanced formulation.

Example 6: Provision of PUFAs to pregnant women.

Two types of PUFA-containing capsules were prepared. The first contained ARA, at 500mg per capsule. These were to be taken one a day. The ARA was provided as a microbial oil, obtained from Gist-brocades, Delft, The Netherlands, under the trade name OPTIMAR™. These capsules had a gelatin coat, and contained 20mg of vitamin E. Similar capsules were also prepared having the same amount (500mg) of DHA, being present as a microbial oil obtained from Martek Corporation, Columbia, United States of America (under the trade name DHASCO™). These capsules were also designed to be taken one per day.

Trials were conducted with pregnant women ingesting either one ARA capsule per day, or one ARA and one DHA capsule per day. The women chosen for the study were those that had been found to have relatively low levels of ARA in the blood. A number of women who were pregnant were therefore tested for *in vivo* ARA blood levels and permission was obtained to take part in the study. The first group of women were teenagers of from 15 to 20 years of age. For all these women, this was their first pregnancy. Due to early maturation they were found to benefit from both ARA and ARA plus DHA supplementation in their diet. Both regimes increased *in vivo* ARA levels.

A second group of women, also pregnant, were studied, these being from age 40 to 50. During pregnancy it was also found their *in vivo* blood levels were increasing under both supplementation regimes. Half of the women chosen in this study were having their fourth child.

Three women each pregnant with twins were chosen for supplementation with one ARA capsule and one DHA capsule per day. Their ARA *in vivo* levels were found to be relatively low, probably because the ARA from the blood of the mother was being absorbed and consumed by both foetuses. These women were supplemented with the ARA and DHA capsules and the ARA levels in the blood were found to increase.

Example 7: Provision of ARA and DHA to subjects with low PUFA content.

The same capsules were used as described in Example 6, except this time the ARA capsules contained only 250mg ARA. These capsules could be taken once or twice daily, according to the subject and their condition.

A number of people were chosen for this study due to their relatively low content of PUFAs in the blood. The reason for the low PUFA content was not always immediately evident. However, it has been found that a number of diseases or adverse conditions lead to low PUFA levels, and it was therefore postulated that providing either a correct dosage of ARA, or a balance of ARA:DHA, the *in vivo* ARA levels could be increased, which might moderate some of the symptoms of the condition. Some of the conditions were thought to result in a poor efficiency in conversion of a precursor to ARA itself, for example a defect or deficiency with the enzyme Δ6-desaturase. Those conditions that were found by the Applicant to often give rise to low PUFA levels included cystic fibrosis, multiple sclerosis, celiac disease and osteoporosis. In addition, patients who were being treated for alcoholism, addiction to drugs or who were immunocompromised (AIDs patients) were also found to have low levels of PUFAs.

A study was therefore made where either one or two ARA capsules were taken daily, to give an ARA:DHA content of either 1:1 or 1:2. In almost all cases those

subjects who were taking these capsules (for at least 3 weeks) were all found to have, at the end of the trial, increased *in vivo* ARA blood levels.

Example 8: Provision of PUFAs in infant formula.

Both solid (powdered) and liquid infant formula baby food was prepared containing 0.5% ARA and 0.5% DHA. This formula was fed to babies regularly in their first three months by mothers who had decided not to breast feed their children. As a control, the *in vivo* ARA blood levels of these children were compared to those that were being breast fed over the same time period. It was found that in the infants being bottle fed that their ARA levels were comparable to those being breast fed.

Comparative Example 9 and Example 10

A number of breast feeding women were chosen for a comparative trial. One group of women were fed two EFANATAL™ capsules per day (to give a daily intake of DHA 125mg, ARA 8.6mg and GLA 40mg). For comparison, a second group of women were given similarly prepared capsules (with a gelatin/glycerol shell) containing 150mg ARA per capsules (to give a daily ARA intake of 300mg ARA,2 capsules per day). In this second group a third capsule was also taken, one per day, which contained DHA at 500mg per capsule.

The ARA levels in the lactating women in both groups, after child birth, was compared. Also compared was the level of ARA in the mothers breast milk.

In the first EFANATAL™ group the ARA levels were found to have decreased markedly in the blood, and to a lesser extent in the breast milk, only two weeks after the trial involving consumption of EFANATAL™ had begun. In contrast those women

taking the two capsules of ARA and one capsule of DHA per day were found to have the ARA levels in their blood increase, and the breast milk levels also increased to above 0.7%.

CLAIMS

1. An edible formulation comprising ARA at an amount adapted to deliver a dosage of from 150mg to 1g/day ARA.

2. A formulation according to claim 1 which is adapted to deliver from 250 to 500 mg/day ARA.

3. A formulation according to claim 1 to 2 which is additionally adapted to deliver DHA.

4. A formulation according to any preceding claim which is adapted to deliver a dosage of from 400 to 600 mg/day DHA.

5. A formulation according to any preceding claim wherein the ratio of ARA:DHA is from 1:5 to 5:1, such as from 1:1 to 1:2.

6. An edible formulation comprising from 150 to 700 mg ARA which is intended to be ingested once per day.

7. An edible formulation comprising from 75 to 350 mg ARA which is adapted to be ingested twice per day.

8. An edible formulation according to any preceding claim which is a food or nutritional supplement.

9. An edible formulation according to any preceding claim which is a pharmaceutical composition.

10. A pharmaceutical composition comprising ARA and DHA at a ratio of ARA:DHA at from 1:1 to 1:2.

11. A foodstuff comprising from 0.1 to 5% ARA.

12. The use of ARA as a dietary or nutritional supplement for a woman who is:

a. pregnant and at an age of from 15 to 20;

b. pregnant and at an age of from 40 to 60, such as from 50 to 55;

c. pregnant with her fourth, fifth or subsequent child;

d. pregnant with twins, triplets or quadruplets;

e. pregnant and is from 1 to 3 months into her pregnancy;

f. pregnant as a result of in vitro fertilisation (IVF) or who is undergoing IVF treatment but not yet pregnant;

g. pregnant at from 20 or more weeks of gestation;

h. pregnant and is malnourished, poorly or marginally nourished, suffering from malnutrition or malabsorption;

i. trying to become pregnant;

j. pregnant, for promoting intra-uterine growth of a foetus; or

k. lactating, for increasing the level of ARA or EPA in the women's breast milk.

13. The use of ARA as a dietary or nutritional supplement for a human who is over 50 years old, preferably over 65 years old.

14. The use of ARA as a dietary or nutritional supplement for a non-human mammal which is pregnant or lactating.

15. The use according to claim 12 wherein the ARA is ingested at from 150 to ~~700, such as from 250 to 500, mg/day.~~

16. The use of ARA for the manufacture of a medicament for assisting in preventing, ameliorating or treating a disease or condition associated with an abnormal or low level of n-3 or n-6 PUFA in the blood.

17. The use according to claim 16 wherein the disease or condition is a neuronal disease, such as schizophrenia, cystic fibrosis, idiopathic immunoglobulin A nephropathy, multiple sclerosis, retinitis pigmentosis, Usher's syndrome, celiac disease, macular degeneration, Parkinsons' disease, osteoporosis, Alzheimer's disease or phenylketonuria.

18. The use of ARA for promoting lactation and/or reproductive efficiency, success or fertility in a human or non-human female mammal.

19. The use of ARA and DHA in an edible formulation at an ARA:DHA ratio that increases the ARA level in blood.

20. The use according to claim 19 wherein the ratio of ARA:DHA is from 1:5 to 5:1.

21. The use according to claim 20 wherein the ratio of ARA:DHA is from 1:1 to 1:2.

22. The use according to any of claims 19 to 21 for a person who is a diabetic, an alcoholic, a drug abuser, smoker or is immunocompromised or has an abnormal immune level.

ABSTRACT

PUFA SUPPLEMENTS

Edible formulations, such as pharmaceutical compositions or nutritional supplements, are disclosed comprising ARA that are adapted to deliver from 150mg to 1g per day of ARA. These formulations may contain additional polyunsaturated fatty acids (PUFAs) for example DHA. The DHA may be given at a dosage of from 400 to 600mg per day, and the ratio of ARA:DHA may be from 1:5 to 5:1. Pharmaceutical compositions comprising ARA and DHA at a ratio of ARA:DHA of 1:1 to 1:2 are also disclosed, as are foodstuffs comprising of 0.1 to 5% ARA. Such formulations can be used to increase ARA levels *in vivo*, for example for pregnant women or for people who have diseases or conditions associated with low ARA levels.